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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,034	SHIZUYA, HIROAKI	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 09 September 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20040510.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement filed 5/10/04 fails to fully comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein as WO 01/11951 has not been considered. Only the first page (cover sheet) of the document was provided.

Claim Objections

Claims 18 and 25-40 are objected to because of the following informalities: In claim 18, "a first and second non-human animal DNA sequences" (line 5) is grammatically improper, and "the human DNA" should be --the human DNA coding sequence--; "human DNA" is initially used as an adjective, not a noun. According to the preamble, claims 25-40 are directed to a method of making a DNA construct. However, the actual process steps of claim 25 go beyond a method of making a DNA construct, i.e. an embryogenic stem cell is made with the construct. Claim 26 adds steps that go even farther beyond the making of a DNA construct, where the ES cell is implanted in a pseudopregnant non-human animal. Consequently, these claims would be more accurately described as method of using the construct, rather than making it. Appropriate correction is required. See warning of duplicate claiming below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 25-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments wherein the non-human animal is a mouse, the non-human animal DNA of the first construct is a mouse genomic DNA comprising mouse DNA that is homologous to the human DNA sequence that is immediately flanked by first and second mouse sequences that are homologous to the flanking first and second mouse genomic DNA sequences that flank the human DNA sequence in the second construct, the embryogenic stem (ES) cell is a mouse ES cell, the non-human blastocyst is a mouse blastocyst, and the pseudopregnant non-human animal is a pseudopregnant mouse, does not reasonably provide enablement for any other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-17 are explicitly directed to making a humanized animal, such as is claimed in claims 41 and 42, and the DNA construct produced by the method of claims 25-40 is taught in the specification as being used to make a humanized animal. The specification (¶ 0048) defines "humanized" animal as being a non-human animal whose genome comprises a human sequence that has replaced analogous, i.e. orthologous, sequences in the genome of the non-human animal.

The claims are broadly directed to methods for introducing a DNA construct (third) into an ES cell of a non-human animal, wherein the DNA construct comprises a human DNA sequence flanked by a first and second non-human animal DNA sequence. The claims do not require that the non-human ES cell and the non-human animal DNA be from the same non-human animal, i.e. the ES cell could be a mouse ES cell, and the non-human animal DNA could be from a horse. Presumably, the non-human animal ES cell is from the same species as the "humanized animal", since it is not possible for a mouse ES cell, for example, to develop into a different animal such as a dog. The claims broadly embrace an ES cell from any non-human animal, such as a mouse, rat, cow, pig, lizard, bird, or cuttlefish. The claims also broadly embrace embodiments wherein the species origin of the ES cell, blastocyst and pseudopregnant non-human animal may be different, e.g. a mouse ES cell, chicken blastocyst, and pseudopregnant horse.

Since the genome of the "humanized" animal must, by definition, contain a human sequence in place of its ortholog in the animal, several constraints are placed on the identity of the various non-human animal DNA sequences and the ES cell recited in the claims. As taught in the specification, the construction of the third construct and the subsequent construction of the ES cell and humanized animal is mediated by homologous recombination (not recombination in general, as recited in the claims, which would include illegitimate recombination) first between the first and second non-human animal sequences of the second construct and their homologs in the first construct, and then by homologous recombination between the non-human animal sequences flanking the human sequences in the third construct and their homologs in the genome of the ES cell (e.g. see figs. 3 and 4). Consequently, the only way the non-human ortholog of the

human DNA can be replaced by the human DNA present in the third construct is if 1) the non-human animal DNA sequence of the first construct is DNA sequence from the same animal as the non-human animal sequences flanking the human DNA sequence of the second and third constructs; 2) the non-human animal DNA sequence of the first construct comprises homologs of the first and second non-human animal sequences of the second construct that in the non-human animal flank non-human animal DNA orthologous to the human DNA sequence of the second and third constructs, and in the same order and orientation as in the second construct and in the genome of the ES cell; and 3) the non-human animal sequences flanking the human DNA sequence in the first, second and third constructs are from the same species of non-human animal from which the ES cell is obtained.

The method being claimed is basically the same as that used to make targeted gene disruptions in an ES cell for subsequently making a knock-out transgenic animal, where genomic DNA is replaced with foreign DNA such as a marker gene. The difference is that instead of a marker gene, the genomic DNA is being replaced with its human ortholog. At the time of filing, the state of the art held that targeted gene disruption could only be carried out in mouse. Gene targeting requires homologous recombination in cells in culture and the only cells in culture that are totipotent and can contribute to the germline, giving rise to a stable transgenic animal, are totipotent mouse ES cells. The art at the time of filing further held that totipotent ES cells capable of giving rise to a germ-line transgenic animal were not available for any species other than mouse. Campbell et al. (Theriogenology, vol. 47, pp, 63-72, 1997) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Wheeler et al.

(Theriogenology, Vol. 56, 1345-1369, 2001) taught putative pig ES cells, which produced pig chimeras but there is no disclosure that the chimera gave rise to a pig of the ES cell phenotype (pages 1351-1352), indicating that the ES cells are not totipotent as they are not germline competent. Further, Wheeler states, in reference to ES cells recently isolated and the production of swine and cattle chimera, "validation of totipotency of these embryo-derived ES cell lines awaits conformation" (page 1351, para. 1, last sentence). Prelle et al. (Cells Tissues Organs, Vol. 165, pages 220-236, 1999) states many embryo-derived cell lines resemble morphologically mouse ES cells, and have the ability to differentiate in vitro, but there is no evidence of live born, fertile germ line chimeras in species other than mouse (page 222, col. 2, para. 1, lines 10-16). The specification provides no guidance on the isolation and use of ES cells of species other than mouse in the context of the claimed invention.

The claims permit the animal species of origin of the ES cell, blastocyst and pseudopregnant non-human animal to be different. However, such implantation is not predictable, as Fehilly et al. (Nature 307: 634-636, 1984) teach that often two unrelated species cannot carry a live hybrid fetus to term due to factors such as placental abnormalities and maternal immunological reaction against foreign antigens of the conceptus which would be the cause of immediate abortion (see p. 634, 2nd column, 2nd paragraph). Fehilly *et al.* summarize experiments for the production of such animals, and show an extremely low percentage of full term young (see Table 1, p. 635). Although Fehilly *et al.* show that is possible to produce embryos that have been implanted into surrogate mothers of a foreign species, it is clearly an unpredictable process. The specification provides no guidance as to how one would use ES cells,

blastocysts and pseudopregnant animals of different species to bring a chimera derived of cells from different animal species to term in a pseudopregnant animals of yet another species.

Therefore, because the specification only teaches gene-targeted replacement and because the prior art teaches that gene targeting can only be performed to make transgenic mice, such a knock-out mice, the specification and art at the time of filing only enable making gene-targeted mice using mouse DNA, mouse ES cells, mouse blastocysts, and pseudopregnant mice.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are introducing the embryogenic stem cells into a non-human blastocyst and implanting the chimeric blastocyst into a pseudopregnant non-human animal, which then carries to term a humanized animal arising from the implanted blastocyst. The preamble of claim 1 indicates that the method is for producing an animal. However, the recited steps would not result in an animal, but result only in a non-human embryonic stem cell comprising the third DNA construct, or in the case of claim 2, a pseudopregnant non-human animal comprising the ES cell in some unspecified location.

Claims 2, 8, 11, 15-24, 26, 32, 35, and 38-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 26 recite the limitation "the embryogenic stem cells" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites an embryogenic stem cell (singular).

Claims 8 and 32 recite the limitation "the human gene sequence" in 1. There is insufficient antecedent basis for this limitation in the claim. In addition, claims recite "sequence is ... genes," and it is unclear if the sequence can comprise a gene or must comprise multiple genes. Also, the list that follows "genes encoding" is a list of proteins and genes. Genes do not encode genes. Also, it is unclear what "insulin receptors immunoglobulins metabolic pathway genes refers to". The list should be recited in the following way "a gene encoding a ..., a ..., a ..., or a ...; a ... gene; a ... gene; a ... gene, and a ... gene", where semi-colons separate the different genes being listed, and commas separate different proteins being encoded by the "gene encoding."

Claims 11 and 35 recite the limitation "the intron" in 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 14 and 38 recite the limitation "the non-human animal DNA sequence" in line 2. There is insufficient antecedent basis for this limitation in the claim. There are two different non-human DNA sequences in the third construct. It is unclear which of these is "the non-human animal DNA sequence" being referred to in claim 14.

Claim 15 recites the limitations "the non-human animal" and "the non-human embryonic stem cells". There is insufficient antecedent basis for these limitations in the claim. With respect to "the non-human animal" it is unclear if this refers to the "humanized animal" of claim 1, or to "non-human animal," which is used as an adjective, from which the non-human animal DNA is

taken. Claim 1 does not require that the non-human animal DNA be from the same source as that of the ES cell, or the humanized animal. With respect to the latter, claim 1 refers to an ES "cell", not "cells."

Claims 16, 17, 39, and 40 are unclear with respect to how the human DNA sequence and the non-human DNA sequence "are joined to" the start or stop codons, and whether the start or stop codons are part of the human DNA sequence or not. It is presumed that the human DNA sequence comprises the start or stop codon at its 5' or 3' end, respectively, to which the first or second non-human animal DNA sequence, respectively, is joined, but that is not what the claims recite.

Claim 18 recites the limitation "the non-human animal" in lines 6-7. There is insufficient antecedent basis for this limitation in the claim.

Claim 23 recites the limitation "the start codon" in line 2. Claim 24 recites the limitation "the stop codon" in line 2. There is insufficient antecedent basis for these limitations in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Stacey et al., Mol. Cell. Biol. 14: 1009-1016, 1994.

Stacey et al. describes a humanized mouse comprising a human α-lactalbumin gene in place of the endogenous mouse α-lactalbumin gene. The targeting vector used to make the mouse was made by a different method than the third DNA construct recited in instant claim 1. However, an analogous mouse made by the method of instant claim 1 would produce a mouse with the same humanized α-lactalbumin gene.

Double Patenting

Applicant is advised that should claims 1-14, 16, and 17 be found allowable, claims 25-40, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The only difference between these two sets of claims is the preamble. However, as indicated in the objection to claims 25-40 above, the recited process steps go beyond the goal set in the preamble, and thus the steps as recited are directed to the same method as that recited in claims 1-14, 16, and 17.

Conclusion

The subject matter of claims 1-40 are free of the prior art of record, which does not disclose or fairly suggest the DNA constructs required by the instant claims. Xie et al. (Nature 406: 435-439, 2000) is representative of most prior art on humanized mice, where the mouse gene is inactivated by targeted disruption, and DNA comprising a human ortholog (or its cDNA)

is inserted at a random location. The resulting mouse does not have the human ortholog in place of the endogenous mouse gene, rather the human ortholog is inserted at an unrelated location in the genome. Other humanized mice have been made by a method represented by Shiao et al., (Transgenic Res. 8: 295-302, 1999) where the mouse ortholog is disrupted by a construct comprising human orthologous DNA, but that is assembled *in vitro* using enzymes, and not by recombination between DNAs such as the first and second constructs of claim 1. The method described in Stacey et al. (described above) for making the targeting vector is significantly different from that being claimed here, but would result in similar humanized mice. In both Shiao and Stacey, the targeting vector is analogous to the second vector used in the claimed method. Neither teach insertion of a selectable marker into an intron present within the human DNA of the targeting vector, as in claim 18. Shiao teaches the prevalent method of inserting the selectable marker between the human DNA and one of the flanking mouse sequences. The method of Stacey requires no selectable marker in the vector for selection of targeted ES cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER